**A comparison of long term outcomes in patients managed with VV-ECMO in the first and second waves of the COVID-19 pandemic in the UK.**

Benjamin E Garfield PhD1,2\*, Paolo Bianchi MD1,2,3\*, Deepa J Arachchillage PhD4,5, Francisca Caetano MD1, Sujal Desai PhD6,7, James Doyle MBChB1, Clara Hernandez Caballero MBBS1, Anne-Marie Doyle DClinPsy1, Sachin Mehta MBChB1, Alexander Law BSc2, Sian Jaggar MD1,3, Maria Kokosi MD6,8, Philip L Molyneaux PhD6,8, Maurizio Passariello MD1, Meena Naja BMBS1, Carole Ridge MBBChBAO6,7, Joana Alçada PhD1,8, Brijesh Patel PhD1,2, Suveer Singh PhD1,6\* Stephane Ledot MD1,2,3\*

\*Equally contributed

1 Department of Adult Intensive Care, Royal Brompton & Harefield Hospitals, part of Guy’s and St Thomas’s NHS Foundation Trust, London, United Kingdom

2 Division of Anaesthetics, Pain Medicine, and Intensive Care, Department of Surgery and Cancer, Imperial College London, London, United Kingdom

3 Department of Anaesthesia, Royal Brompton & Harefield Hospitals, part of Guy’s and St Thomas’s NHS Foundation Trust, London, United Kingdom

4 Centre for Haematology, Department of Immunology and Inflammation, Imperial College London, London, United Kingdom

5 Department of Haematology, Royal Brompton & Harefield Hospitals, part of Guy’s and St Thomas’s NHS Foundation Trust, London, United Kingdom

6 National Heart and Lung Institute, Imperial College London, London, United Kingdom

7 Department of Radiology, Royal Brompton & Harefield Hospitals, part of Guy’s and St Thomas’s NHS Foundation Trust, London, United Kingdom

8 Dept of Respiratory Medicine, Royal Brompton & Harefield Hospitals, part of Guy’s and St Thomas’s NHS Foundation Trust, London, United Kingdom

**Corresponding author:** Dr Benjamin Garfield, Department of Adult Intensive Care, Royal Brompton Hospital, Sydney Street, London, UK, SW3 6NP, [b.garfield@rbht.nhs.uk](mailto:b.garfield@rbht.nhs.uk)

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**Key words:** COVID-19, ARDS, ECMO, Quality of life, Pulmonary function

**Abstract**

**Objective**

Early studies of veno-venous extracorporeal membrane oxygenation (VV-ECMO) in COVID-19 have revealed similar outcomes to historical cohorts. Changes in the disease and treatments has led to differences in the patients supported on VV-ECMO in the 1st and 2nd waves. We aimed to compare these two groups in both the acute and follow-up phase.

**Design**

Retrospective single-center cohort study comparing mortality at censoring date (30/11/2021) and decannulation, patient characteristics, complications and lung function and quality of life (QOL – by EQ5D3L) at first follow-up in patients supported on VV-ECMO between wave 1 and wave 2 of the COVID-19 pandemic.

**Setting**

Critical care department of a severe acute respiratory failure service

**Patients**

Patients supported on ECMO for COVID-19 between wave 1 (17/03/2020-31/08/2020) and wave 2 (01/09/2020-25/05/2021).

**Interventions**

None

**Measurements and Main Results**

One-hundred and twenty-three patients were included in our analysis. Survival at censoring date [Chi-squared 6.35, p=0.012] and decannulation [90.4% vs 70.0%, p<0.001], was significantly lower in the 2nd wave, whilst duration of ECMO run was longer [12.0(18.0-30.0) days vs. 29.5(15.5-58.3)] days (p=0.005)). Wave 2 patients had longer application of non-invasive ventilation (NIV) prior to ECMO and a higher incidence of barotrauma. Patient age and NIV use were independently associated with increased mortality [OR 1.07(1.01-1.14), p=0.025 and 3.37(1.12–12.60), p=0.043 respectively]. QOL and lung function, apart from KCOc was similar at follow up across the waves.

**Conclusions**

Most patients with COVID-19 supported on ECMO in both waves survived in the short and longer term. At follow-up patients had similar lung function and QOL across the 2 waves. This suggests that ECMO has an ongoing role in the management of a carefully selected group of patients with COVID-19.

**Key points**

**Question:** We aimed to define the differences in longer term outcomes of COVID-19 patients supported on VV-ECMO between wave 1 and wave 2 of the pandemic.

**Findings:** This single-center retrospective study revealed worse outcomes in terms of long-term survival but similar quality of life and lung function at follow up in the 2nd wave compared to the 1st.

**Meaning:**Despite increased mortality important long term outcomes in survivors of COVID-19 remain similar between those supported in wave 2 compared to wave 1.

**Introduction**

Veno-venous (VV) Extracorporeal Membrane Oxygenation (ECMO) is an established salvage intervention in patients with refractory respiratory failure [1].

The use of ECMO support in patients presenting with COVID-19 related respiratory failure has been a matter of debate [2]. However, analysis of a large multi-centre cohort of patients treated with ECMO during the first wave of the pandemic has shown outcomes comparable to that noted in randomized control trials [3]. Furthermore, our single center 6-months outcome data suggest survival rates similar to our historical cohort of patients with viral pneumonia [4].

There has been a rapid expansion of knowledge around pathophysiology [5], management and outcome of patients with COVID-19. We have seen the emergence of new variants [6, 7], witnessed the discovery of effective treatments including dexamethasone and interleukin-6 (IL-6) inhibitors [8, 9], the rollout of mass vaccination programs [10] and the widespread use of non-invasive ventilation (NIV) [11]. This has clearly been accompanied by a change in the effectiveness of ECMO on a global scale [12], with later cohorts experiencing lower short-term survival [13-15].

Whilst 90 and 180-day survival in patients supported with ECMO for COVID-19 has been extensively documented [4, 13, 14, 16] important outcomes like long-term survival, follow up pulmonary function and quality of life (QOL) have only recently been reported in the literature [15, 16].

Despite our increased knowledge the COVID-19 pandemic seems far from over, with a surge in cases in China, since the lifting of the zero COVID policy [17]. Therefore, the need to understand which patients with COVID-19 will benefit most from ECMO has continued relevance.

We aimed to compare the differences between the patients managed in our center across the 1st and 2nd waves of the pandemic in the UK, from referral through admission and in those who survived to recovery.

Our hypothesis was that patients in the 2nd wave of the pandemic would have a higher mortality on ECMO, but would have similar quality of life and lung function if they survived to follow-up. The increased mortality may be due to patients in the second wave having failed to respond to evidence based treatments established after the first wave.

**Materials and Methods**

This is a single-centre retrospective cohort study of an intensive care unit providing ECMO services to 46 referring hospitals within a wider national network [18]. All patients admitted with polymerase chain reaction proven COVID-19 pneumonitis requiring admission, ventilation, proning and VV-ECMO support were identified. Patients supported with ECMO with a known outcome of decannulation or death as of 30/11/2021 (censoring date) were included in the analysis.

The pandemic waves were defined as per the national intensive care audit system (ICNARC) in the United Kingdom (UK) (1st: 17/03/2020-31/08/2020 and 2nd: 01/09/2020-31/05/2021) [19]. Patients were excluded from the analysis if they were under 18 years of age or if they required veno-arterial ECMO.

The study was approved by the Derby Research Ethics Committee (20/EM/0204) and the need for individual informed consent was waived due to the retrospective nature of the analysis.

Patient’s suitability for VV-ECMO was assessed in line with national UK commissioning criteria described by Camporota *et al.* [20]. Data were collected from electronic patient records and referral documents as previously described [4]. A full explanation of data collection methods can be found in the online supplement. Data on lung function, which was performed as per American thoracic society guidelines [21] and QOL, measured by EQ-5D-3L [22] was collected at first follow-up.

The primary outcome of the study was difference in mortality at censoring date between patients supported on VV-ECMO for COVID-19 ARDS in the 1st and 2nd waves. Secondary outcomes included differences in pulmonary function and quality of life at first follow up, mortality at decannulation and pre-defined ECMO related complications. We also examined differences in duration of ECMO run. A long run was defined as ≥30 days. Finally, we performed logistic regression to examine the predictors of mortality at decannulation in the cohort as a whole.

Data were analysed using Graphpad Prism (Graphpad, San Diego, USA) and R Studio (RStudio, Vienna, Austria) as previously described [4] a detailed account of which can also be found in the supplementary material.. There was no imputation undertaken for missing data, and we adopted a strategy of using all valid data to increase the sample size of our study as advocated by Dzuria and colleagues [23]. As convention, statistical significance was set at a p value <0.05.

**Results**

One-hundred and twenty-three patients with COVID-19 pneumonitis were supported with VV-ECMO during the study period (wave 1:53 vs. wave 2:70).

Whilst monthly referrals during the pandemic waves remained similar there were significant differences in the proportions of patients with COVID-19 admitted to our hospital requiring different types of advanced ventilatory support (supplementary table 1).

Patient demographics are shown in supplementary table 2. Body mass index (BMI) was significantly higher in the 2nd wave compared to the 1st.

Baseline referral characteristics are shown in table 1. In the 2nd wave patients had longer duration of NIV prior to intubation and lower Murray scores. Patients in the 2nd wave also had a higher incidence of barotrauma, with pneumomediastinum being more common than pneumothorax. Those patients who had barotrauma at referral had a longer duration of NIV than those without [5 (2-7) days vs 1 (0–5) days, p=0.007]. Patients in the 2nd wave were also more likely to have been given dexamethasone, an IL-6 inhibitor and remdesivir prior to ECMO.

Admission characteristics in the first 24 hours after initiation of ECMO are shown in supplementary table 3. Patients in the 2nd wave had lower admission sequential-organ-failure-assessment (SOFA) scores, creatinine levels, d-dimers, lactate dehydrogenase (LDH) and C-reactive protein (CRP). They also had higher albumin. There was no difference in ventilatory practice in the first 24 hours between the 1st and 2nd wave.

Differences in ECMO related complications, between the 1st and 2nd wave are shown in table 2. The only significant differences between the groups was an increased incidence of pulmonary embolism (PE) in the 1st wave. Alongside this there was an increased proportion of patients in the 2nd wave being pulsed with iv methylprednisolone whilst on ECMO [47.2% vs 70.0%, p=0.015].

The duration of ECMO run was significantly shorter in the 1st wave when compared to the 2nd [12 (18-30) vs. 30 (16-58) days (p=0.005)] (Figure1A), with more long runs in the 2nd wave [18.9% vs. 48.6%, p<0.001] (Figure1B).

Significantly more patients in the 1st wave survived to decannulation [(90.6% vs. 70.0% (p=0.007)] (Figure2A) and to censoring date (Figure2B). No patients underwent lung transplantation.

Supplementary table 4 shows the differences in referral and admission characteristics in those that survived and did not survive to decannulation. Significant differences were found in patients age, duration of NIV prior to ECMO and the RESP score. In logistic regression both age [OR 1.07 (1.01-1.14, p=0.025] and use of NIV [OR 3.37 (1.12–12.60), p=0.043] were independently associated with increased risk of mortality on ECMO.

Follow up lung function was available in 32 patients in wave 1 and 25 patients in wave 2 at a median time from admission of 7.6 (3.0–9.6) and 7.5 (7.0–7.9) months respectively. The transfer coefficient of carbon monoxide corrected for haemoglobin (KCOc) percent predicted was significantly higher in the patients in wave 2 compared to wave 1. There were no other significant differences in lung function between the groups (Figure3A). Example CT scans showing the resolution of COVID-19 changes are shown in Figure 3C. Follow up QOL was available in 27 patients in wave 1 and 25 patients in wave 2 at a median time from admission of 7.9 (5.8–8.6) months and 7.4 (6.3–8.2) months respectively. There was no difference in indexed quality of life scores between the two groups at follow up (Figure 3B). Proportionally more patients in wave 2 had ongoing problems with mobility, self-care and usual activities but this did not reach statistical significance (Supplementary table5).

**Discussion**

In this comprehensive view of the 1st and 2nd wave of the COVID-19 pandemic we have shown that patients supported on VV-ECMO in the 2nd wave had an increased mortality and longer ECMO runs than patients in the 1st wave. Although regional and referral variations clearly exist our data is supported by International registry data, showing that ECMO outcomes worsened over time [12, 15]. We have also, demonstrated that pulmonary function and quality of life is similar, between survivors of the 2 waves at an average of 7 months follow up.

In the UK, ICNARC reported a new increase in ICU admissions due to COVID-19 after 01/09/2020, defining the 2nd wave of the pandemic [19]. The results of several studies, particularly the REMAP-CAP trial, changed the standard of care for patients with COVID-19 admitted to hospital between the 1st and 2nd waves. Dexamethasone [8], and anti-IL-6 drugs [9, 24], have been shown to improve mortality, whilst remdesivir [25] reduced time to recovery. The adoption of these treatments is well represented in our baseline characteristics, with steroids, remdesivir and IL-6 inhibition emerging as the 2 waves progressed. These interventions along with vaccination [13] have undoubtedly improved global outcomes in patients presenting to hospital with COVID-19 [19] but are not universally effective in preventing some patients from developing severe disease [17] and requiring ECMO. Furthermore, the emergence of vaccine evading strains, the waning efficiency of vaccines and the unvaccinated continue to pose a risk to global health [26].

Patients in the 2nd wave had lower inflammatory markers at cannulation, likely due to an alteration in host response to different COVID-19 variants and previous steroid treatment [27]. They were also more likely to receive a pulse of methylprednisolone once on ECMO, for non-resolving COVID-19 pneumonitis. Whilst the optimum timing of immunomodulation remains uncertain [28] one potential explanation of the lack of steroid responsiveness seen in the 2nd wave may have been pre-treatment with dexamethasone in the early phase of their disease prior to initiation of ECMO. [13]. A factor that may have had a significant effect on mortality.

A further difference seen between the 1st and 2nd waves is a reduction in the incidence of PE on comupterised tomography pulmonary angiogram (CTPA). This is probably due to more patients receiving treatment dose anticoagulation very early in the disease [29], along with the increase use of immunomodulators [8, 9]. The reduction in burden of pulmonary vascular disease in the 2nd wave could be a factor in the significant difference in KCOc between the 1st and 2nd waves at follow up. Further work focusing on the effect of longer term anticoagulation (3–6 months) in patients with COVID-19 and proven PE should be undertaken.

As well as changes in pharmacological interventions, studies have suggested that NIV could prevent intubation and reduce mortality in COVID-19 ARDS [11]. We found a longer duration of NIV in patients supported on ECMO in the 2nd wave. These findings were mirrored across the rest of the National ECMO service [20], possibly due to a reduced concern about aerosolisation and a wish to avoid intubation where possible, allowing time for patients to respond to disease modifying treatment. Duration of invasive mechanical ventilation prior to ECMO represents a well-established risk factor for increased mortality [30], whilst duration of NIV is less well studied. Our findings suggest that in COVID-19 duration of NIV may be associated with reduced survival in patients going on to require VV-ECMO. These findings are supported in the wider literature [31, 32]. The increased duration of NIV in patients in the 2nd wave meant these individuals may have been more likely to be exposed to self-induced lung injury and delayed institution of prone positioning [33]. This hypothesis is supported by the association between barotrauma and NIV duration in our cohort.

Survival data demonstrated that very few patients who survived to 90-days died during the follow up period. This finding was independent of whether the patient was supported in the 1st or 2nd wave and is in keeping with data on longer term survival after ECMO from other causes of ARDS [1] and COVID-19 .

Despite the reduction in survival between the 1st and 2nd waves, mortality in both groups remains similar to historical cohorts [3, 4]. The better survival rates reported in our cohort than in the general literature could be partly due to the high volume of patients supported in our center [34]. In contrast to our data a study reporting the outcomes of patients referred but deemed not suitable for ECMO has shown a mortality of 80% at 90 days [35]. With mortality in our 2nd wave cohort of just more than 30%, our findings highlight the importance of VV-ECMO in supporting a carefully selected group of patients with COVID-19 ARDS.

As well as showing the differences in outcome over the pandemic our data also sheds some light on who might benefit most from support with VV-ECMO for COVID-19. Age is an important predictor of mortality in patients with COVID-19 who are managed with VV-ECMO both in our study and the wider literature [3]. The RESP score was developed to predict outcomes on ECMO [30] and despite the narrow range seen in our population, was still significantly higher in those who survived compared to those who died. Our data therefore validates the RESP score as a tool which can predict survival on ECMO even within a narrow window.

The median duration of ECMO was 11 days longer in the 2nd wave than the 1st. This has been verified in a number of other studies [36]. As well as implication for individuals and families these longer runs have economic implications with every day of ECMO support costing over $7500 in one study [37], making it a huge financial burden, particularly in resource poor healthcare settings. Interestingly, nearly half the patients in the second wave of the pandemic had ECMO runs of longer than 30 days. In the original case series some patients were transplanted, only after 34 days on ECMO [38]. We argue that our data suggest that in some cases early transplant may be deleterious to long term outcomes and that further work is needed to determine the optimum timing for declaring non-resolution in this new disease [39]*.*

Follow up data on patients supported on VV-ECMO for COVID-19 is lacking [40], with data limited to working status and symptoms evaluated by questionnaire [16]. Here we present a well characterized unique cohort of patients who had lung function and quality of life measured at follow up. We have demonstrated that there is very little difference in the follow up parameters of patients supported in the 1st and 2nd waves. This suggests that despite the reduction in survival across the 2 waves, patients who survive to follow up have similar physiological reserve and QOL. This adds weight to the argument that ECMO is a worthwhile treatment in a carefully selected group of patients with COVID-19. Whilst there was no statistical difference in QOL between the 2 waves there were some numerical differences in the proportion of patients reporting mobility, self-care and usual activity issues. This may relate to an increase in critical care-neuro-myopathy precipitated by a longer duration of ECMO run, ICU stay and increased use of steroids [41]. The use of alternative cannulation strategies, early tracheostomy and active rehabilitation may help obviate these differences in outcomes in future cohorts. The QOL in our survivors is typical of that seen in patients after ARDS due to COVID-19 and other causes [42, 43] and is lower, numerically at least, than a healthy population of the same age who have an expected EQ5D3L index score of 0.8 [44]. As well as the aforementioned increased KCOc in the 2nd wave the lung function parameters at follow up in our group as a whole show a disproportionate reduction in transfer factor of carbon monoxide (TLCOc) with relatively preserved spirometry. This is in keeping with follow up data from the wider ARDS and COVID-19 literature [42, 43] and may be due to persistent perfusion defects seen in some patients at six month follow up after COVID-19 pneumonitis [45].

**Limitations and Strengths**

This study’s limitations include its single-center and retrospective design. There is also the issue of missing data. Data was collected from referral forms which included both data entry boxes and free text, a potential source of bias. Due to the nature of the study it was not possible to control for multiple comparisons, accepting that this may cause more type 1 error. The effect of vaccination is not taken into account in this study. This study does not cover the outcomes of patients referred for ECMO but deemed too well or too unwell to benefit. This data is presented elsewhere [46]. Whilst there were differences in the proportion of patients requiring advanced respiratory support between the waves, bed occupancy with critically ill patients remained high limiting the influence of these differences on outcomes for our ECMO patients. Finally the change in guidance between the first and second waves [20] is likely to have restricted access to ECMO to those who might benefit more improving not reducing survival across the pandemic.

Despite these limitations this is a large single-center ECMO study incorporating a homogenous group of patients, with a similar disease profile and a uniform approach to clinical management.

**Conclusions**

Our study shows a reduced survival and longer ECMO run in the 2nd wave of the COVID-19 pandemic.

Those who survived in both waves had similar quality of life and lung function at follow up. Age and NIV use are important predictors of mortality in our cohort and pose important questions about the optimum duration of a trial of NIV.

Despite the poorer outcomes as the global pandemic progresses [15, 17], our results support the continued provision of ECMO in a carefully selected population of patients with ARDS secondary to COVID-19.

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**Figure Legends**

**Figure 1 a)** *Duration of ECMO run in the 1st and 2nd waves.* ***b)*** *Number of patients in the 1st and 2nd waves with short (< 30 days) and long (≥ 30 days) duration of ECMO run.*

**Figure 2 a)** *Differences in survival to decannulation in patients with COVID-19 supported with veno-venous extracorporeal membrane oxygenation (VV-ECMO) in the 1st and 2nd wave of the pandemic.* **b)** Differences in survival to censure date 30th November 2021 *in patients with COVID-19 supported with veno-venous extracorporeal membrane oxygenation (VV-ECMO) in the 1st and 2nd wave of the pandemic.*

***Figure 3 a)*** *Pulmonary function tests at follow in patients with COVID-19 supported on ECMO in the 1st and 2nd waves. Forced expiratory volume in 1 second (FEV1) [82.9±20.1% vs.76.8±15.6], Forced vital capacity (FVC) [80.4±20.7% vs. 76.2±15.6], transfer factor of carbon monoxide corrected for haemoglobin (TLCOc) [59.5±17.8 vs. 60.2±15.5], transfer coefficient of carbon monoxide corrected for haemoglobin (KCOc) [80.1±16.2 vs. 90.7±13.0].* ***b)*** *Follow up EQ5D3L quality of life index in patients with COVID-19 supported on ECMO in the 1st and 2nd waves (note the normalised value for this age group in the UK is 0.8).* ***c)*** *Representative admission and follow up CT scans of 2 patients supported on ECMO for COVID-19, one from the 1st wave and one from the 2nd wave.*